JAMA | Review

New-Onset Seizure in Adults and Adolescents
A Review

Jay R. Gavvala, MD, MSCI; Stephan U. Schuele, MD, MPH

IMPORTANCE Approximately 8% to 10% of the population will experience a seizure during their lifetime. Only about 2% to 3% of patients go on to develop epilepsy. Understanding the underlying etiology leading to an accurate diagnosis is necessary to ensure appropriate treatment and that patients with low risk for recurrence are not treated unnecessarily.

OBSERVATIONS Patients can present with new-onset seizure for a variety of reasons such as acute symptomatic seizures due to acute brain injury or metabolic derangements, or unprovoked seizures that are the initial manifestation of epilepsy. A patient history and physical examination may identify features more consistent with an epileptic event and laboratory studies and brain imaging can identify an acute insult contributing to the presentation. Patients diagnosed with first-time unprovoked seizure require electroencephalography and epilepsy protocol–specific magnetic resonance imaging of the brain, which includes thin-cut coronal slices to determine risk of recurrence and the need for long-term treatment. In patients who meet the criteria for diagnosis of epilepsy, a carefully selected antiepileptic medication with consideration of comorbidities, adverse effect profile, and type of epilepsy is essential along with appropriate counseling.

CONCLUSIONS AND RELEVANCE Approximately 3% of the population will develop epilepsy but 2 to 3 times as many patients will experience a single seizure or seizure-like event. A diagnosis of epilepsy has significant medical, social, and emotional consequences. A careful patient history and physical examination, electroencephalography, and brain imaging are necessary to separate patients with acute symptomatic seizures, single unprovoked seizures, and nonepileptic events from those with new-onset epilepsy.

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Author Affiliations: Department of Neurology, Baylor College of Medicine, Houston, Texas (Gavvala); Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Schuele).

Corresponding Author: Jay R. Gavvala, MD, MSCI, Department of Neurology, Baylor College of Medicine, 7200 Cambridge 9A, Houston, TX 77030 (jay.gavvala@bcm.edu).

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Approximately 8% to 10% of the population will experience a seizure during their lifetime. Only about 2% to 3% go on to develop epilepsy.[1] Patients presenting with a suspected first-time unprovoked seizure should undergo an orderly evaluation.[2,3] The first step is to distinguish the presenting episode from other paroxysmal events that can mimic seizures, which can include migraine, transient ischemic attack, and syncope (**Table 1**).[2] The second step is to assess for provocative factors such as acute systemic disturbances or acute insults to the brain that would predispose a patient to acute symptomatic seizures.[4] In the absence of such triggers, a comprehensive workup after a first seizure is required to establish risk of recurrence and necessity of antiepileptic treatment.

The previous definition of epilepsy was based on a patient having at least 2 unprovoked seizures more than 24 hours apart; however, the current definition includes patients with "one unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%) occurring over the next 10 years."[5] This definition applies to patients with evidence of an epilepsy syndrome on an electroencephalogram or a significant symptomatic etiology on magnetic resonance imaging (MRI) of the brain,[5,6] emphasizing the importance of access to and quality of additional testing.

This review will focus on the evaluation of new-onset seizure in adults and adolescents, which includes history and physical examination, the differential diagnosis, characteristic features of each etiology, and features of a rational diagnostic workup. The choice of treatment includes discussion of the consideration of efficacy, adverse effects, dosing, and patient counseling.

Methods

The literature published through November 2016 was reviewed by searching PubMed. The following keywords were used: *epilepsy, first time seizure, unprovoked seizures, first time unprovoked seizure, acute symptomatic seizure, antiepileptic treatment, seizure epidemiology, epilepsy epidemiology, women with epilepsy, epilepsy in the elderly, sudden unexplained death in epilepsy,* and *refractory epilepsy*. No language restriction was applied. Review articles, primary literature, and meta-analysis were included in this review. Articles were reviewed if they were published between 1976 and 2016. Articles were rated using

the Oxford Centre for Evidence-based Medicine 2009 levels of evidence and grading scale recommendations for clinical practice (Box).[7] A total of 99 articles were included in this review.

Definitions

Seizure: A transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Unprovoked Seizure: Occurring in the absence of precipitating factors and may be caused by a static or progressive injury.

Acute Symptomatic Seizure: In close temporal association with a transient central nervous system or systemic insult presumed to be an acute manifestation of the insult.

Focal Seizure: Initial onset originates within 1 part of a cerebral hemisphere.

Generalized Seizure: Initial activity is consistent with rapidly engaging networks distributing in bilateral cerebral hemispheres.

Epilepsy: Disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. Has been defined as 2 or more unprovoked seizures occurring more than 24 hours apart or 1 unprovoked seizure and a high risk (at least 60%) of recurrent unprovoked seizures over the next 10 years.

Results

Clinical Presentation

The diagnosis of an epileptic seizure or epilepsy is largely based on clinical history. The clinical features of seizures vary according to the underlying neuroanatomy.[8] The goal of obtaining a patient's seizure history is to determine if the event was likely epileptic, and if so, to distinguish between seizures with a focal and generalized onset. Based on their presumed clinical and electrographic onset pattern, seizures are classified as generalized (involving bilateral neural networks) or focal (involving neural networks present in 1 lobe or hemisphere) (Table 1).[6] Although many events may in fact be seizures, the differential diagnosis for paroxysmal neurological disorders, particularly if the initial event is unwitnessed, can be broad and includes migraine, syncope, transient ischemic attack, psychogenic nonepileptic seizures, movement disorders, sleep disorders, and panic attacks (Table 1).[2,9]

Epidemiology

Population-based studies from the 1980s and 1990s suggested that there was a lifetime risk of 8% to 10% for unprovoked or acute symptomatic seizures and a 2% to 3% chance of actually developing epilepsy.[10,11] More recent studies have shown an incidence of acute symptomatic seizures of 29 to 39 per 100 000 per year, an incidence of a single unprovoked seizure of 23 to 61 per 100 000 per year, and an incidence of epilepsy worldwide of 50.4 per 100 000 per year.[1,12] In 2011, this resulted in an estimated 1.6 million emergency department (ED) visits for evaluation of seizures and approximately 400 000 patients with new-onset seizures presenting to the ED.[13]

Risk Factors for Epilepsy

Patient age at onset and a family history of epilepsy are helpful to narrow in on a likely etiology and epilepsy syndrome. Excessive sleep deprivation and use of alcohol and illicit drugs can be precipitating factors for a seizure. Furthermore, certain medications (clozapine, cephalosporins, fluoroquinolones, bupropion, and tramadol) have been shown to reduce the seizure threshold; therefore, a patient's medication list should be carefully screened for these medications. Metabolic derangements, altered homeostasis due to organ failure, and toxin exposure are also common provoking factors for seizures.[3,14] Review of medical and surgical histories are pertinent in the search for acute symptomatic causes and other possible etiologies. Questions about the patient's childhood development such as complications during delivery, history of central nervous system infections, head injuries (particularly those with loss of consciousness), and history of central nervous system disease or prior neurological surgeries are important in characterizing a patient's risk for future seizures.

Assessment and Diagnosis

Additional testing is necessary for a patient with new-onset seizure to (1) assess if the patient likely had an acute symptomatic seizure, (2) support the clinical suspicion that the event was epileptic and estimate the risk of recurrence, and (3) determine the type of seizure and the most appropriate choice for treatment. In the following subsections, the utility and appropriateness of several commonly ordered tests for patients with new-onset seizures are discussed.

History and Physical Examination

The diagnosis of epilepsy and epileptic seizures largely remains a clinical one that is highly dependent on the patient history and physical examination. The initial focus of the history should be the patient's experience, recollection, and awareness of the event. Subjective symptoms at the onset of a seizure are considered auras, which are typically seen in patients with focal seizures, and provide the most localizing information of where in the brain seizures might arise. It is necessary for clinicians to ask patients about prior events that may represent seizure symptoms. A large number of patients who experience a first convulsive seizure may also have had prior staring spells, myoclonic jerks out of wakefulness, or stereotypic events (such as auras) and would meet the criteria for the diagnosis of epilepsy or even a specific epilepsy syndrome.

In many cases, the patient has impaired awareness during the event and witness accounts are crucial. It is important to evaluate and document patient and witness accounts separately. Doing so enhances the accuracy of the report, and is often the basis of distinguishing physiological impairment from nonphysiological events (such as when a patient claims awareness of bilateral shaking movements that hardly occur during epileptic seizures without amnesia and unresponsiveness, raising concern of a nonepileptic etiology).

A description of all relevant physical examination findings is beyond the scope of this article. A thorough physical examination is important. Examination of the oral mucosa may reveal lateral tongue bites. In pooled studies, lateral tongue bites are seen in about 22% of patients with all types of epileptic seizures, whereas these bites are not seen in patients with psychogenic nonepileptic seizures.[15] Bruises or scrapes over the body may be seen after falls, and back pain may indicate a vertebral compression fracture. Evidence of nuchal rigidity or asterixis suggests an underlying systemic disorder that may have caused an acute symptomatic seizure. Transient or persistent focal weakness or asymmetry on examination suggests areas

Table 1. Differential Diagnosis of New-Onset Seizure

Clinical Entity	Clinical Features	Tools for Diagnosis	Patient Account	Bystander Account
Transient ischemic attack	Results from temporary interruption of blood supply in the distribution of a cerebral vessel. This produces rapid onset of negative symptoms such as numbness, weakness, and aphasia, and is typically not associated with stiffness or jerking. Occasionally a transient ischemic attack may present with a stuttering course.	Risk factors for cerebrovascular disease. Brain magnetic resonance imaging and magnetic resonance angiogram looking at blood vessels of the head and neck.	Fully aware of deficits and typically only is limited in his or her ability to report the presentation due to language impairment.	Same as patient account unless the patient has language impairment preventing accurate reporting.
Migraine	Aura present with visual aura, unilateral pulsating headache, nausea, and vomiting. However, atypical migraines can present with isolated neurological symptoms or without associated headache. The duration and intensity of migraines typically last hours to days with a slow progression of aura and neurological deficits.	A history of migraines and family history of migraines may be helpful.	Does not lose awareness during a migraine and can accurately report his or her presentation. However, confusional and basilar migraines can result in inattention and decreased levels of consciousness.	Similar to patient account unless there is associated confusion or inattention as can be seen in basilar or confusional migraines.
Syncope	A transient loss of consciousness with complete return to preexisting neurological function. Vasovagal syncope typically has a situational trigger such as fear, pain, medical procedures, coughing, micturition, defecation, or Valsalva maneuver. Orthostasis can aggravate a vasovagal reaction or bring out a syncope from hypovolemia or structural heart disease.	Electrocardiography, cardiac telemetry, and echocardiography are recommended to exclude cardiac etiologies. Tilt table testing may help reproduce typical events.	Typically is preceded by feelings of dizziness, fullness in ears, nausea, and blurry vision. Patients are usually pale and have cold and clammy skin and flaccid muscle tone. Patients will not have recollection of events that occur after loss of consciousness, although this period is brief. There is typically no postictal state.	May notice brief myoclonic jerks or tonic posturing at the end of the event. This may be described by witnesses as "convulsive" activity.
Psychogenic nonepileptic seizures	Typically are associated with emotional events or stressors, last longer than epileptic seizures, and often have a waxing and waning quality. Clinical features such as eye closure, pelvic thrusting, vocal stuttering, and partial awareness during whole-body motor movements are typical.	Continuous electroencephalographic monitoring is recommended to capture events in question and ensure no epileptic changes are seen.	May claim awareness of bilateral shaking movements, which in epileptic seizures are typically associated with amnesia and unresponsiveness.	May report clinical features of the event such as those most typical for psychogenic nonepileptic seizures (eye closure, pelvic thrusting, waxing and waning of motor movements).
Focal seizure	May start with an aura followed by loss of awareness, unilateral sensations, or motor activity. This may progress to a generalized tonic-clonic seizure in some cases (evolving to bilateral convulsive activity). This progression is faster than seen with migraine.	An electroencephalogram may show focal epileptiform discharges. Brain magnetic resonance imaging should be performed to look for structural abnormalities.	May report an aura (déjà vu or an epigastric aura with temporal lobe epilepsy), contralateral paresthesia in parietal lobe seizures, and visual distortions in occipital lobe seizures. If awareness is not affected, he or she may report progression of symptoms to unilateral motor or sensory symptoms. If loss of awareness or generalized tonic-clonic activity, will not be able to report event.	Report probably more reliable and may include patient staring, frequent eye blinking, semipurposeful movements of hands and feet, and characteristics of tonic-clonic seizure activity. May also report open eyes, urinary incontinence, focal or whole-body stiffening, postevent lethargy or confusion, and a stereotyped progression with recurrent events.
Generalized seizure	Typically no warning. Seizures characterized by brief staring spells, generalized tonic-clonic activity, myoclonic jerks.	An electroencephalogram may show generalized epileptiform discharges and confirm a specific epilepsy syndrome.	Frequently have no awareness of event, except for myoclonic jerks, but may report postictal findings such as tongue bite or incontinence (if generalized tonic-clonic seizures).	Crucial to understand the clinical presentation.

Box. Levels of Evidence and Grading Scale Used for Article Rating[a]

Levels of Evidence

Level 1

A: Systematic review with homogeneity of randomized clinical trials

B: Individual randomized clinical trial with a narrow confidence interval

C: All or none case studies (ie, those in which a series of people with the risk factors all experience the outcome or those in which all do not experience the outcome)

Level 2

A: Systematic review with homogeneity of cohort studies

B: Individual cohort study

C: Outcomes research

Level 3

A: Systematic review with homogeneity of case-control studies

B: Individual case-control study

Level 4

Case series

Level 5

Expert opinion

Grading Scale Recommendations

Grade A: Consistent level 1 evidence studies

Grade B: Consistent level 2 or 3 evidence studies or extrapolations from level 1 studies

Grade C: Level 4 studies or extrapolations from level 2 or 3 evidence studies

Grade D: Level 5 evidence studies or troublingly inconsistent or inconclusive studies of any level

[a] Defined by the Oxford Centre for Evidence-based Medicine.[7]

of brain dysfunction that could predispose a patient to have seizures, which should be confirmed with brain imaging. Examination of the skin may reveal signs of a neurocutaneous syndrome associated with epilepsy such as neurofibromatosis, tuberous sclerosis, and Sturge-Weber syndrome.[16,17]

Brain Imaging

Patients with a first seizure should have neuroimaging; however, uncertainty remains regarding the appropriate timing and type of imaging (grade B).[18,19] Earlier literature suggested approximately 10% of patients with new-onset seizures had abnormalities revealed by imaging that were believed to be clinically relevant; however, most of these studies exclusively used computed tomography (CT).[18] With greater use of MRI, the detection rate of abnormalities believed to contribute to a patient's occurrence of seizures was closer to 30%.[20] Emergency neuroimaging is recommended when a serious structural brain lesion is suspected as well as for new neurological deficits, persistent altered mental status, recent trauma, and prolonged headache.[19]

Computed tomography is the usual first imaging modality due to its ease of access and should be considered for patients with new-onset seizures seen in the ED. However, CT scans may miss certain lesions such as low-grade gliomas, hippocampal sclerosis, cavernous malformations, and malformations of cortical development (eg, cortical dysplasia or periventricular heterotopias).[21,22] If there is sufficient concern for a focal abnormality based on the progression of clinical signs and symptoms (seizure semiology) or physical examination, further imaging with an MRI is warranted. In patients who return to baseline after a first unprovoked seizure, have a normal examination in the ED, and normal emergency brain imaging (CT, emergency MRI, or both) results, further imaging with an epilepsy protocol–specific brain MRI should be performed in conjunction with evaluation by a neurologist or epileptologist.

An epilepsy protocol–specific brain MRI differs from a typical MRI in that it includes thin 1- to 3-mm slices and coronal fluid–attenuated inversion recovery sequences that offer additional sensitivity over standard protocol MRIs for the detection of subtle lesions, particularly focal cortical dysplasia and hippocampal sclerosis.[23-25] The presence of those often subtle abnormalities signifies a risk for seizure recurrence of greater than 60% and establishes a diagnosis of epilepsy.[6] Use of an epilepsy protocol–specific MRI and review of the imaging results by an expert neuroradiologist can increase the sensitivity in detecting abnormalities.[25]

Electroencephalography

Most patients with new-onset seizure who do not return to baseline neurological function within 30 to 60 minutes after the end of a seizure, have a waxing and waning level of consciousness, or have focal dysfunction unexplained by a structural lesion should be considered for hospital admission and continuous electroencephalographic monitoring. Continuous electroencephalographic monitoring has been increasingly used with growing recognition for patients with seizures that have subtle or no clinical signs. In patients with subclinical seizures, less than 50% are detected by routine 30-minute electroencephalographic monitoring but the yield increases to greater than 90% with 24- to 36-hour continuous electroencephalographic monitoring in patients with an acute brain injury and mental status change.[26] However, even among patients who return to baseline neurological function, almost one-quarter admitted to the hospital after new-onset seizure had additional risk factors identified during the hospitalization that suggested a high likelihood of seizure recurrence.[27]

Standard 30-minute electroencephalographic monitoring after new-onset seizure is helpful to determine the likely seizure type (focal vs generalized) and to determine the risk of recurrence after a first event (grade B).[28-30] In patients with new-onset seizure, 29% of patients will have epileptiform abnormalities on their first electroencephalogram.[18] There does appear to be a slightly higher yield of epileptiform abnormalities on electroencephalograms performed in patients within 24 to 48 hours of new-onset seizure.[31-33]

In a patient who has fully recovered and is considered for discharge, electroencephalography can be safely delayed if the treatment does not depend on the electroencephalographic result. A recent study that assessed 20-year outcomes found an increase in mortality and recurrence following a first generalized tonic-clonic seizure in patients with a known structural etiology.[34] However, in patients without a structural abnormality, recognizing an underlying epileptogenic focus or the electroencephalographic pattern of a particular epilepsy syndrome may be easier and more expertly

done while the patient is an outpatient. This may also reduce the confounding factors of an inpatient admission, such as medication effects or acute postictal electroencephalographic changes, and provide a more accurate representation of a patient's inherent risk for seizure recurrence.

Even in patients with apparent acute symptomatic seizures, it is important to not overlook the importance of electroencephalography or brain imaging. Older data suggest that up to 30% of patients with suspected alcohol withdrawal seizures had a potentially epileptogenic structural abnormality related to a traumatic injury.[35] Conversely, a large number of adult patients with a first acute symptomatic seizure are found to have electroencephalographic abnormalities suggestive of a genetic predisposition for generalized seizures, which may have only manifested with additional triggers.[36]

Emergency electroencephalography is indicated when a patient does not return to baseline neurological function within 30 to 60 minutes after the end of a seizure, has a waxing and waning level of consciousness, or has focal neurological dysfunction that is unexplained by a structural lesion. In all other cases, nonemergent electroencephalography is recommended, ideally within 24 to 48 hours of the new-onset seizure.

Chemistry Panel

Routine screening of patients after new-onset seizure for hypoglycemia, uremia, drug intoxication, and hyponatremia has been proposed (grade D). These recommendations are largely based on patients seeking care in the ED with a higher frequency of acute symptomatic seizures.[37,38] In the one prospective study evaluating patients with new-onset seizures, only 4% of patients had relevant laboratory findings of hyperglycemia and hyponatremia.[38] In outpatient clinic–based studies, laboratory findings were of limited utility and no significant results were seen.[39]

Prolactin Level

Elevated serum prolactin level has been measured in patients after the seizure event. If the pretest probability of a patient having an epileptic seizure is 50% or greater, prolactin level has a positive predictive value of greater than 93% in differentiating generalized or focal seizures with impaired consciousness from psychogenic nonepileptic seizures if a patient's prolactin level is measured 10 to 20 minutes after a suspected event (grade B). However, prolactin level measured after the seizure event has to be compared with the patient's baseline prolactin level measured at least 6 hours prior to the suspected event, which is rarely done, making prolactin level analysis generally impractical for clinical use. Furthermore, prolactin elevations can also be seen with a syncopal event and thus cannot differentiate between an epileptic seizure and syncope (grade B).[40]

It is also important to note the low sensitivity and low negative predictive value of prolactin level analysis, making it insufficient in diagnosing patients with psychogenic nonepileptic seizures or for excluding patients with epileptic seizures with impairment of consciousness (grade A).[40] Prolactin level analysis can be effective in distinguishing between patients with seizures that involve impairment of consciousness and psychogenic nonepileptic seizures, but only if prolactin level is measured 10 to 20 minutes after a suspected event and is compared with a baseline prolactin level measured at least 6 hours prior to the suspected event. Serum prolactin level analysis is not an effective test to distinguish seizure from syncope.

Lumbar Puncture

Lumbar puncture should be considered in cases with concern for meningitis, encephalitis, or subarachnoid hemorrhage. No study has examined the systematic use of lumbar puncture in patients presenting with new-onset seizures (grade D). In studies from the ED in which clinical reasoning guided the use of lumbar puncture, up to 8% of patients were found to have clinically significant findings.[18] Even though these findings were almost always found in patients with high clinical suspicion of central nervous system infection, in rare cases immunocompromised patients (such as those with human immunodeficiency virus) had abnormal lumbar puncture results without overt clinical evidence of central nervous system infection.[41]

Risk of Seizure Recurrence

Unprovoked Seizures

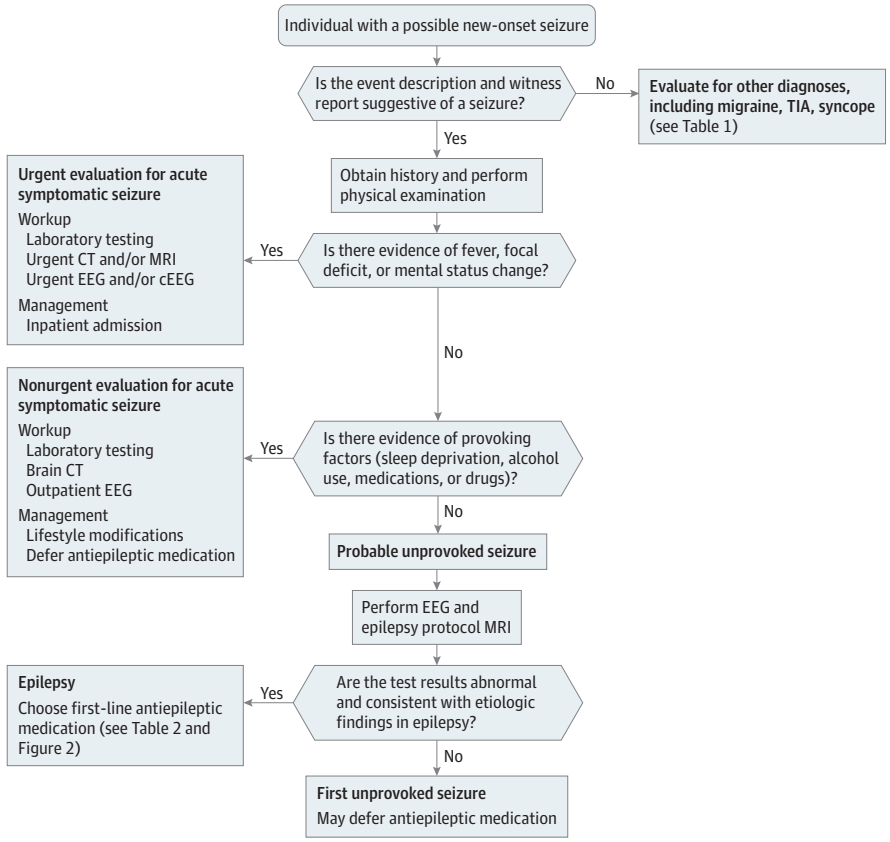
A recent American Academy of Neurology practice guideline summarized the current data on prognosis and therapy after new-onset seizure.[42] There is an approximately 35% chance of a seizure recurrence within 5 years following new-onset seizure in adults.[11,43-45] However, in persons who have had a second seizure, the risk of a recurrent seizure increases to 75% during the following 5 years.[44,46] Patients with an abnormal neurological examination, abnormal brain imaging (grade B), an electroencephalogram with epileptiform abnormalities (grade A), nocturnal seizure (grade B), or seizures attributed to a prior brain injury (grade A) consistently have a much higher risk of seizure recurrence.[11,18,42,43,46] Individual studies were highlighted in the American Academy of Neurology practice guideline as representative examples of the increased risk of seizure recurrence. Patients with seizures attributed to a prior brain injury had 2.55 (95% CI, 1.44-4.51) times the rate of seizure recurrence based on 5-year recurrence rates increasing from 29% to 48% compared with patients with seizures not attributed to a clear cause.[42,47]

Patients with abnormal brain imaging results had 2.44 (95% CI, 1.09-5.44) times the risk for seizure recurrence during the subsequent 4 years (from 47% to 89%) compared with those with normal imaging results.[42,48] Patients with generalized spike wave epileptiform abnormalities on an electroencephalogram were 2.16 (95% CI, 1.0-4.3) times more likely to have seizure recurrence during the following 5 years based on recurrence rates increasing from 26% to 58% compared with those without epileptiform abnormalities.[42,47] Patients who experienced seizures at night were 2.1 (95% CI, 1.0-4.3) times more likely to have seizure recurrence based on 3-year recurrence rates of 33% increasing to 54% compared with patients who experienced seizures during wakefulness.[42,49] Other factors such as the patient's age, type of seizure, and family history of seizures have not been consistently validated and are of uncertain practical significance.[43]

Acute Symptomatic Seizures

The qualities of provoked seizures (acute symptomatic seizures) are not as well characterized but clearly portend a lower risk in patients for subsequent unprovoked seizures. Patients with seizures resulting from acute brain insults have a recurrence risk for seizures of 10% to 20%. This includes patients with seizures resulting from a severe closed head injury, acute hemorrhagic and ischemic stroke, subarachnoid hemorrhage, brain surgery, and central nervous system infections.[50] An electroencephalogram obtained during the acute period showing epileptiform activity increases the

Figure 1. Suggested Systematic Approach to Patients With New-Onset Seizure



This algorithm presents the key clinical questions and workup needed in the evaluation of a patient suspected of having new-onset seizure. This approach is a suggestion for how to evaluate patients based on the authors' experience and has not been validated. This is meant as a general recommendation for an evaluation of a patient with new-onset seizure; however, individual cases may deviate from this algorithm. CT indicates computed tomography; cEEG, continuous electroencephalography; EEG, electroencephalography; MRI, magnetic resonance imaging; TIA, transient ischemic attack. A checklist version of this algorithm appears in eAppendix 1 in the Supplement.

likelihood in patients for recurrent acute symptomatic seizures, but is not predictive for future unprovoked seizures.[50]

Treatment

A seizure can be a terrifying experience with significant medical, emotional, and social consequences. There is a natural desire by patients, families, and clinicians to prevent another seizure by empirically starting antiepileptic medications even though two-thirds of patients with new-onset seizures do not warrant treatment. When considering treatment, clinicians need to have an understanding of the risk of seizure recurrence, seizure type and etiology, suitable choice of antiepileptic medication, and anticipated duration of treatment. A suggested algorithm for treatment of new-onset seizure is outlined in **Figure 1** and for new-onset epilepsy in **Figure 2**.

Choice of Antiepileptic Medication

The ideal first prescribed antiepileptic medication should be efficacious, well tolerated, and easy for clinicians to prescribe and patients to take. There are many available antiepileptic medications that can be considered for first-line monotherapy in adults with epilepsy,[51] each with its advantages and limitations (**Table 2**).

The choice of antiepileptic medication is primarily based on the presumed type of epilepsy.[51,52] Antiepileptic medications can be divided into broad-spectrum and narrow-spectrum agents. Narrow-spectrum agents are typically effective in patients with all forms of focal seizures regardless of alteration of consciousness or secondary generalization. However, some narrow-spectrum agents may worsen myoclonic and absence seizures in patients with genetic generalized epilepsies, such as absence epilepsy and juvenile myoclonic epilepsy.[53] Broad-spectrum agents improve seizures in patients with focal epilepsy and most generalized epilepsies, but often with variable efficacy directed at specific seizure types.[16,51,52] Lamotrigine has been reported to worsen myoclonic seizures, topiramate has not been shown to be effective against absence seizures, and zonisamide has limited evidence supporting its effectiveness in myoclonic or absence seizures.[52,54] Use of a broad-spectrum agent is recommended for patients if there is insufficient evidence pointing to a focal onset.[55]

Another important consideration when making an antiepileptic medication choice is the time to therapeutic onset. This is particularly important (1) in the inpatient setting in patients found to have frequent seizures that warrant rapid antiepileptic medication administration and (2) in the ED if the goal is to get a patient to a therapeutic dose prior to discharge. Medications considered for first-line monotherapy and available in intravenous preparation include fosphenytoin, valproate, levetiracetam, and lacosamide (only labeled for adjunctive use in Europe).

Special Considerations

The choice of antiepileptic medication should account for the patient's comorbidities, other medication use, age, sex, and the cost of the medication. Older antiepileptic medications such as phenytoin and carbamazepine are potent inducers of the cytochrome P450 system and valproate is an inhibitor, resulting in possible drug-drug

interactions. In patients with multiple comorbidities, or taking medications such as warfarin or chemotherapeutic agents, use of newer antiepileptic medications such as levetiracetam, lamotrigine, or lacosamide with limited drug interactions is favored. Another important consideration is if the patient has liver or renal dysfunction that would result in impaired elimination of an antiepileptic medication.[51,55]

Generic Formulations

With the rising costs among health care systems, there has been increasing use of generic formulations. Although the US Food and Drug Administration requires manufacturers of generic formulations to have bioequivalence to the original brand-name product with the same active ingredients, prior retrospective studies and case reports have suggested that seizure control and rates of adverse effects change after substitution with a generic antiepileptic medication.[56,57] Even though the generic formulation has bioequivalence to the brand-name product, the differences between generic formulations may have greater than expected differences in plasma drug concentrations.[58] However, 3 recently completed studies (2 of which were prospective randomized clinical trials) showed no difference in bioequivalence when switching from a brand-name product to a generic product or between multiple generic products.[59-61]

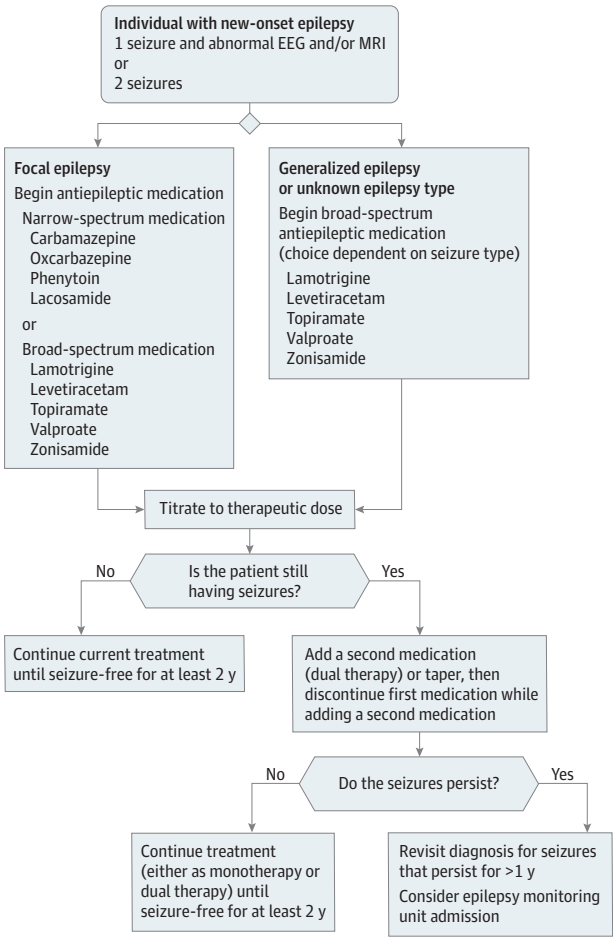
Comparative Trials

Comparative efficacy of the available antiepileptic medications is limited. An earlier study comparing older antiepileptic medications found that phenytoin and carbamazepine offered the highest treatment success in patients with focal epilepsy, although phenytoin had more adverse effects (grade A).[62] Valproate and carbamazepine were found to have similar effectiveness in the treatment of patients with focal seizures evolving into bilateral convulsive seizures; however, carbamazepine was found to have better control of focal seizures with fewer adverse effects (grade A).[63] Subsequent studies showed similar efficacy of lamotrigine, oxcarbazepine, and carbamazepine in patients with newly diagnosed focal epilepsy, although lamotrigine was better tolerated (grade A).[64] In patients with generalized epilepsies, valproate was found to be more efficacious than lamotrigine and better tolerated than topiramate (grade A).[65] More recent studies have shown levetiracetam and zonisamide to be both efficacious and well tolerated in the treatment of patients with focal and generalized epilepsy (grade A).[66,67]

Adverse Effects

In patients taking their first antiepileptic medication after new-onset seizure, adverse effects were seen in 7% to 31% of all patients.[42] In patients with epilepsy, especially those receiving polytherapy, the number of adverse effects is significantly higher and was up to 88% according to 1 study.[68] It is important for clinicians to ask about adverse effects at each office visit because patients are less likely to report them unless directly asked.[29,69,70] Most commonly, patients experience somnolence, dizziness, blurry vision, and difficulties with concentration and memory.[69] Typically these are dose-dependent adverse effects and are most prominent during the first few days of therapy. Slower dose escalations or giving lower scheduled doses but more frequently timed (eg, 100 mg of phenytoin 3 times/day vs 150 mg of phenytoin twice daily) may be beneficial in alleviating these effects.

Figure 2. Suggested Treatment Algorithm in Patients With New-Onset Epilepsy



This algorithm is a suggested approach to treatment and has not been validated. This is meant as a general recommendation; however, individual cases may deviate from this algorithm. Further information on the specific antiepileptic medications appears in the Table 2. *Unknown epilepsy type* refers to a type of epilepsy for which the data are inconclusive as to whether the seizures were focal or generalized in origin. EEG indicates electroencephalography; MRI, magnetic resonance imaging. A checklist version of this algorithm appears in eAppendix 2 in the Supplement.

All antiepileptic medications can cause a rash, ranging from a mild erythematous maculopapular rash to severe reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.[69] Antiepileptic medications most commonly associated with development of a rash are phenytoin, carbamazepine, and lamotrigine. Approximately 1 to 10 per 10 000 patients newly taking antiepileptic medications will develop severe cutaneous reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.[69] More than 90% of all patients who develop toxic epidermal necrolysis and Stevens-Johnson syndrome developed symptoms within the first 60 days of therapy so clinicians should be especially vigilant during this period and advise patients and families of warning signs.[71]

Recent studies have highlighted the effect of genetic polymorphisms in the development of cutaneous adverse drug reactions, in particular the association of *HLA-B*15:02* alleles with the development of Stevens-Johnson syndrome or toxic epidermal necrolysis

Table 2. First-Line Antiepileptic Medications

Name of Medication[a]	Initial Titration Instructions	Target Maintenance Dose, mg/d[b]	Type of Seizure	Quick Onset?[c]	Advantages	Disadvantages
Narrow-Spectrum Medications[d]						
Carbamazepine	Twice daily increase of 200 mg to target dose over 1-4 wk	800-1200	Focal	No	Large amount of high-quality evidence demonstrating its effectiveness, low cost, has mood stabilizer properties	Enzyme inducer, can worsen generalized epilepsies (particularly myoclonic and absence seizures), risk of skin hypersensitivity, hyponatremia, agranulocytosis
Eslicarbazepine	Once daily dose of 400 mg, increase by 400-600 mg each week	800-1200	Focal	No	Unique mechanism of action compared with other agents, easy titration, once daily dosing	Hyponatremia
Gabapentin[e]	Start with 300-900 mg per day, increase over 1-2 wk	900-1800	Focal	No	No hepatotoxicity, well tolerated in older patients (aged ≥65 years), nonenzyme inducer, effective for neuropathic pain, low risk of skin hypersensitivity reactions	Weight gain, limited evidence of efficacy (except in older patients aged ≥65 years)
Lacosamide[f]	Start with 100 mg twice daily, increase by 100 mg total every week	300-400	Focal	Yes	Intravenous formulation, no hepatotoxicity	Limited evidence of efficacy, dizziness, arrhythmias
Oxcarbazepine	Twice daily dose of 300 mg, increase to target dose over 1-2 wk	1200	Focal	No	Lower potential of enzyme induction, lower risk of rash than carbamazepine	Higher risk of hyponatremia than carbamazepine, can worsen generalized epilepsies (such as myoclonic and absence seizures)
Phenytoin	Dose of 100 mg 3 times per day, increase to target every 3-5 d	300-600	Focal	Yes	Strong evidence of efficacy, low cost, rapid titration, intravenous formulation	Enzyme inducer, high interaction rate, gingival hyperplasia, leukopenia
Broad-Spectrum Medications[g]						
Lamotrigine	Daily dose of 25 mg daily for 2 wk, 50 mg daily for 2 wk, 100 mg daily for 2 wk, then can increase by 50 mg every 1-2 wk[h]	250-350	Focal, most generalized	No	Nonenzyme inducer, no significant interactions, effective for bipolar depression, efficacious in older patients (aged ≥65 years)	Slow titration, interactions with valproate and estrogen-containing compounds, has been reported to worsen myoclonic seizures, risk of rash, Steven-Johnson syndrome
Levetiracetam	Start with 500 mg twice daily, increase by 500 mg every 1-2 wk to target dose	1000-2000	Focal, most generalized	Yes	Nonenzyme inducer, no significant interactions, rapid titration, intravenous formulation available	Risk of psychiatric adverse effects
Topiramate	Dose of 25 mg twice daily, increase by 25-50 mg every week	200-400	Focal, most generalized	No	Low enzyme induction potential, effective in migraine prophylaxis	Slow titration, can cause metabolic acidosis, renal stones, paresthesias, cognitive adverse effects, teratogenic effects, ineffective against absence seizures
Valproate	Dose of 250 mg twice daily or 3 times per day, increase dose by 250-500 every week	500-1500	Focal, most generalized	Yes	Rapid titration, mood stabilizing properties, no skin hypersensitivity reactions, migraine prophylaxis, strong evidence of efficacy, intravenous formulation	Enzyme inhibitor, significant risk of teratogenic effects, weight gain, thrombocytopenia, tremor
Zonisamide	Dose of 100 mg daily, increase by 100 mg every 2 wk	200-400	Focal, most generalized	No	No hepatotoxicity, long half-life, can be given as once daily dose	Can cause metabolic acidosis, renal stones, paresthesias, cognitive adverse effects, weight loss

[a] This list is not meant to be exhaustive, but is intended to provide information regarding first-line antiepileptic medications.

[b] Indicates range recommended for new patients.

[c] "Yes" indicates onset within 24 hours and requires use of intravenous formulations of the listed medications.

[d] Designed for patients with specific types of seizures such as focal seizures.

[e] Not commonly thought of as a first-line agent for seizures; however, it has been reported to be effective as monotherapy in older patients (aged ≥65 years).

[f] Only labeled for adjunctive use in Europe.

[g] Have some effectiveness in patients with a wide variety of seizure types (focal plus most generalized seizures).

[h] Use slower titration schedule if patient has concurrent valproate use; can increase titration if patient taking enzyme-inducing antiepileptic medication.

associated with carbamazepine or phenytoin in patients of Asian descent.[72,73] In fact, the Food and Drug Administration mandates screening for *HLA-B*15:02* in all persons of Asian descent prior to initiation of carbamazepine therapy. Patients should be advised to promptly report development of a rash and consideration should be given for a hospital admission or urgent dermatologic evaluation. Offending antiepileptic medications should be promptly withdrawn to prevent progression of an adverse effect.[69]

Antiepileptic Medication Use in Females

In women of childbearing age, it is necessary to consider the antiepileptic medication's potential for teratogenic effects and interactions with contraception. Several antiepileptic medications, most notably P450 inducers, have been shown to increase the clearance of oral contraceptives, possibly resulting in unplanned pregnancies. Furthermore, oral contraceptives have been shown to decrease the plasma concentrations of lamotrigine, leading to fluctuations of lamotrigine levels during a women's ovulatory cycle.[74] It is important for patients to choose alternative methods of contraception or use continuous oral contraceptives without placebo dosing. Intrauterine devices seem to be the best method for contraception in this population because they are the most effective form of contraception and use of these devices enables avoidance of the drug-drug interactions seen between hormonal contraception and many antiepileptic medications.[75]

Valproate is well known for its potential teratogenic effects with an estimated 10% risk for major congenital malformations.[76-78] Recent studies have also demonstrated that children of women taking valproate during pregnancy have lower IQs, memory, and verbal function.[79] Major congenital malformations also have been shown with use of phenobarbital, topiramate, phenytoin, and carbamazepine.[77,78] Females taking levetiracetam and lamotrigine have a risk of major congenital malformations similar to the general population.[76-78] Few articles in the literature have commented on incidence of minor congenital malformations or obstetric complications. The frequency of these malformations and complications seem to be increased with use of antiepileptic medications based on older literature.[80] There is limited evidence of the potential teratogenicity with use of newer antiepileptic medications such as lacosamide and oxcarbazepine.[76-78]

Antiepileptic Medication Use in Older Patients

Changes in pharmacokinetics, concurrent medical illnesses, and lower tolerability of antiepileptic medications pose challenges to prescribing antiepileptic medications in older patients (aged ≥65 years). The limited literature available found lamotrigine and gabapentin to have fewer adverse reactions and have good efficacy.[51,81,82] Levetiracetam also has been recommended for use due to its lower adverse effect profile and higher 1-year retention rate than carbamazepine or valproic acid.[82,83]

Response Rates

Initial studies suggested early initiation of antiepileptic therapy may alter the natural history of epilepsy and improve seizure control. However, 2 large randomized clinical trials looking at immediate vs delayed initiation of antiepileptic therapy after patients experienced new-onset seizure found that while immediate treatment delayed the time to another seizure, long-term prognosis was not affected by delayed initiation of therapy (grade A).[42,45,84] In patients diagnosed with epilepsy after 2 or more unprovoked seizures, approximately 50% will become seizure-free after starting the first appropriately dosed antiepileptic medication. The likelihood of patient freedom from seizures declines with increased number of antiepileptic medication regimens, with 13% becoming seizure-free after initiation of a second antiepileptic medication and 4% after initiation of a third antiepileptic medication.[85]

Patient Counseling

The treatment of a patient after new-onset seizure should include counseling about the medical and social consequences of seizures and safety considerations.[29] It is important for patients to understand the distinction between new-onset seizure and new-onset epilepsy as well as their type of seizure, risk of recurrence, and a discussion of underlying etiology if known. Counseling should include factors that may lower seizure threshold such as sleep deprivation, alcohol intake, drug use, strobe lights, and stress.[3] Patients should also be specifically counseled to avoid working at heights and working with heavy machinery. Persons with epilepsy are 15 to 19 times more likely to die of drowning compared with the general population and high-risk activities should be avoided such as scuba diving, climbing, unobserved swimming, and taking tub baths (patients should be encouraged to take showers instead).[3,86]

Sudden unexpected death in epilepsy is defined as a sudden unexpected witnessed or unwitnessed mortality in otherwise healthy patients with epilepsy with or without evidence of a seizure, in which postmortem examination does not reveal a cause of death.[87] Based on inpatient recordings, sudden unexpected death in epilepsy appears to result from an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by generalized tonic-clonic seizures.[88] Sudden death in persons with epilepsy occurs at a rate 20 times higher than in the general population.[87] Although sudden unexpected death is more likely in patients with epilepsy and large numbers of generalized tonic-clonic seizures, it rarely has occurred in patients with infrequent seizures or after a first seizure.[87,89]

Driving restrictions vary from state to state. In the majority of states, physicians are not required to report patients who have a seizure history to the motor vehicle administration.[90] In the states in which physicians are not obligated to report patients directly to the motor vehicle administration, patient counseling should focus on the risks for driving with a history of seizures and the legal rules and responsibilities for driving, such as the duty to self-report. These discussions should be documented in the patient's medical record.[91]

Most states allow noncommercial driving to resume in patients 6 months after an unprovoked seizure and 3 months after an acute symptomatic seizure. Commercial driving after an unprovoked seizure is usually not permitted until patients are free of seizures for at least 2 to 5 years.[3]

Duration of Therapy

After a period in which a patient is free from seizures, it is reasonable to consider withdrawal of the antiepileptic medication. In the largest study (n = 1013) evaluating withdrawal of antiepileptic medications in patients with epilepsy who had been seizure-free for at least 2 years, 59% remained seizure-free 2 years after weaning of medications.[92] Factors associated with successful remission included being

seizure-free for more than 2 years while taking antiepileptic medications and a normal neurological examination (grade A).[92,93]

In a more recent study evaluating adults with focal epilepsy, a seizure-free period of less than 4 years before withdrawal and a longer duration of active epilepsy were independent risk factors for seizure relapse following withdrawal of antiepileptic medication. The highest risk of relapse appears to be during the first 2 years with less than 1% of relapses occurring more than 5 years after withdrawal of antiepileptic medication.[94] Persistent electroencephalographic abnormalities and structural lesions are associated with a higher risk of relapse and any weaning of medications in these cases should be approached more cautiously.[95]

In patients with acute symptomatic seizures, the likelihood of unprovoked seizures (ie, the risk of developing epilepsies) is low and any use of antiepileptic medications is for the prevention of additional acute symptomatic seizures. In patients with relatively treatable and self-limited derangements (or metabolic abnormalities), antiepileptic medication use could be limited to 7 days if that amount of time is sufficient to correct the abnormality. In patients with an acute brain insult, the prophylaxis is sometimes extended from 1 month to 6 months.[4,50]

Discussion

Making the initial diagnosis of epilepsy has significant medical, social, and emotional consequences. Although many patients will experience only a single seizure, a careful patient history and physical examination and appropriate use of electroencephalography and neuroimaging will help differentiate patients who have alternative diagnoses from the ones at risk for recurrent seizures. Figure 1 is a broad overview of the treatment approach for patients with new-onset seizure. This can serve as a practical guide; however, it is important to realize that patients are not always easily categorized and decisions such as whether to start an antiepileptic medication should be individualized with careful consideration of the risks and benefits by the patient, family, and treating physician.

Several medical centers have explored the benefits of new-onset seizure clinic that would be staffed by epileptologists as a mechanism to bypass long wait times for a neurology evaluation and the ordering of relevant tests. Early studies from Canada have suggested that this model is effective in reducing wait times for appointments, in increasing the speed of diagnostic test completion, and in making an earlier and more accurate diagnosis with approximately 40% of patients meeting criteria for a diagnosis of epilepsy at the initial visit.[96,97] One of these studies found that of children referred to the clinic, one-quarter were incorrectly diagnosed as having a seizure and the diagnosis of epilepsy was missed in more than one-third.[97] Further data, particularly in the adult population, are needed to validate whether this approach is an effective model to emulate on a larger scale.

The American Academy of Neurology recently published a practice guideline summarizing the prognosis and therapy after patients experience new-onset seizure. Patients with an abnormal neurological examination, MRI, electroencephalogram, or a nocturnal seizure had a much higher risk of seizure recurrence.[42] It must be noted that the guideline included a meta-analysis that pooled cases of both treated and untreated patients with new-onset seizure, which were the basis of some of the recommendations, limiting the guideline's strength and its applicability. The specific combination of electroencephalographic and imaging findings necessary to make the diagnosis of epilepsy after new-onset seizure is unclear. It would be overly simplistic to assume that a single seizure plus a lesion or a single seizure plus epileptiform spikes on an electroencephalogram automatically satisfy the criteria for diagnosis of epilepsy. Conflicting evidence from prior studies on seizure recurrence rates in the presence of epileptiform electroencephalographic patterns shows risks both above and below the 60% threshold.[98,99]

High-quality data demonstrating the risk of recurrent seizures in patients with specific types of imaging abnormalities are lacking and very few studies evaluate patients who have both structural imaging and electroencephalographic abnormalities. Future research should focus on the use of predictive models to better characterize the potential additive effects and timing of clinical variables such as seizure etiology, electroencephalographic findings, and brain imaging as it pertains to seizure recurrence.

Conclusions

Approximately 3% of the population will develop epilepsy but 2 to 3 times as many patients will experience a single seizure or seizure-like event. A new diagnosis of epilepsy has significant medical, social, and emotional consequences. A careful patient history and physical examination, electroencephalography, and brain imaging are necessary to separate patients with acute symptomatic seizures, single unprovoked seizures, and nonepileptic events from those with new-onset epilepsy.

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Concept and design: Both authors.
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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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